ANTICANCER ACTIVITY OF PERILLIC DERIVATIVES

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Introduction: Perilllic derivatives have been investigated by antitumoral activities. Perilllic acid may be produced by oxidation of the exocyclic methyl group in the limonene molecule by the yeast \textit{Yarrowia lipolytica} under optimized conditions. Objectives: To obtain R-perilllic acid R-PA) and its sodium salt [(R)-NAP] and, along with commercial (S)-PA, (S)-NAP and (S)-perillyl alcohol, assay the inhibition of leukemia K562, leukemia Lucena, melanoma SKMEL28, and breast carcinoma MCF7 human lines proliferation. Additional studies were performed with (R)-NAP using HT-29, HCT-116 and Caco-2 colon adenocarcinomas cells. Material and Methods: (L)-perilllic acid was obtained by converting (R)-limonene with \textit{Y. lipolytica} ATCC 18942 during 48h. Extraction of the final broth with ethyl acetate led to R-PA that was transformed to R-NAP by sodium methoxide in methanol. Cancer cells were maintained in DMEM in exponential growth phase. Aliquots (100 µl; 5x10\textsuperscript{4} cells/ml) were added to 96-wells plate by 24h before the treatment with the compounds. Compounds were dissolved in DMSO or 0.9% saline and then diluted in DMEM with FBS, 1000 U/I penicillin, streptomycin (0.1 mg) and gentamicin (0.05 mg/ml) and tested in concentrations between 0.01 to 100 µM. Colon adenocarcinoma cells were assayed using (R)-NAP in the range 1.0 to 5.0 mM. Positive controls were conducted in parallel (formaldehyde-induced 0%). After 48h, MTT was added and the cell viability was measured by formazan formation and IC\textsubscript{50} determined. Results and Discussion: (R)-NAP inhibited the Leukemic K562 (IC\textsubscript{50} 1.24 µM) and Lucena cells (IC\textsubscript{50} 0.013 µM), and HCT-116 (IC\textsubscript{50} 3.4 mM). Solubility issues impaired tests with HT-29 (IC\textsubscript{50} > 5.0 mM). Conclusion: Sodium perillate was the most active perilllic derivative tested against the human cancer cell lines tested and could be a represent a new option in the cancer treatment.